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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/982,284 12/01/97 LUBON H 030523/0141

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON DC 20007-5109

HM12/0830

EXAMINER

HAUDA, K

ART UNIT

PAPER NUMBER

1632

13

DATE MAILED:

08/30/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
08/982,284

Applicant(s)
Lubon et al.

Examiner
Karen M. Hauda

Group Art Unit
1632



☒ Responsive to communication(s) filed on June 11, 1999 and August 3, 1999

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1, 5-8, 11-13, and 15-66 is/are pending in the application.

Of the above, claim(s) 16-44 and 66 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1, 5-8, 11-13, 15, and 45-65 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5, 7, 10

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ *Notice to comply w/ Sequence Rules*

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group I, claims 1-15 in Paper No. 9 filed June 11, 1999 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden for the examiner to search group II, drawn to a method of degrading or detoxifying organic material in vivo or in vitro. This is not found persuasive because the method of group II does require an additional search burden of determining the detoxification capabilities of the detoxifying compounds and requires a search for in vitro detoxification which is not required in searching the invention of group I.

The requirement is still deemed proper and is therefore made FINAL.

The preliminary amendment filed August 3, 1999, paper # 11 has been entered. Claims 1-66 are pending.

Claims 16-44 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 9.

Newly submitted claim 66, filed in the preliminary amendment received August 3, 1999, paper # 11 is directed to an invention that is independent or distinct from the invention originally elected in the response received June 1, 1999, paper # 9 for the following reasons:

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Claim 66 is directed to urine which is a patentably distinct product from that of the elected transgenic animal and method of making the transgenic animal. Furthermore, urine is classified in class 424, subclass 76.6 which requires an additional search burden from that of the originally elected invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 16-44 and 66 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 5-8, 11¹³, 15 and 45-65 are under examination.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given THREE MONTHS from the date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37

11/14
8/27/99

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CFR 1.136(a). In no case may an applicant extend the period for response beyond the SIX MONTH statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-8, 11-13, 15 and 45-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-human transgenic mammal whose genome comprises an nucleic acid sequence comprising a mammary specific promoter operably linked to a gene encoding a protein of interest, wherein expression of said protein by somatic cells in said transgenic mammal results in the production of said protein in the urine of said transgenic mammal; or a transgenic mouse whose genome comprises an nucleic acid sequence comprising a uroplakin II promoter operably linked to a gene encoding a protein of interest, wherein expression of said protein by somatic cells in said transgenic mouse results in the production of said protein in the urine of said transgenic mouse; and methods of producing the same, does not reasonably provide enablement for any and all transgenic animals whose genome comprises any and all genes encoding any and all exogenous proteins. The specification does not enable any person skilled in

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the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 5-8, 11-13, 15 and 45-65 are directed methods of producing a non-human transgenic mammal or animal such that a protein is expressed in the urine of said mammal or animal. The art of producing transgenic animals has proven to be an unpredictable one. The level of skill in the transgenic art is such that one cannot predict whether a transgene that is expressed in a mouse will also be expressed efficiently in another non-human animal. For example, Strojek and Wagner (Genetic Engineering, 1988) taught that a high degree of expression of a transgene in a mouse is often not predictive of a high expression in other species, including pigs and rabbits, because for example, the cis acting elements may interact with different trans-acting factors in these other species. Given such species differences in the expression of a transgene, it would be difficult to predict from the results in a mouse the levels of transgene product in another transgenic non-human animal, the consequences of that production, and therefore, the resulting phenotype. Houdebine (Journal of Biotechnology, 1994) discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (page 275, column 1, 1st paragraph). Wall (Theriogenology, 1996) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements and may result in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Wall also discloses the unpredictability of gene integration and expression. At page 61, he states, "Our lack

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of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior.” Additionally at ape 62, he states that “transgene expression and the physiological consequences of transgene products in livestock are not always accurately predicted in transgenic mouse studies.” Additionally, Kappel et al. (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). Furthermore, Ebert et al. (Molecular Endocrinology, 1988) disclose the production of transgenic mice expressing human somatotropin regulated by the mouse metallothionein promoter at levels sufficient to cause an increase in growth; however, expression of the same transgene in pigs did not produce pigs exhibiting the same phenotypic result (page 277, Introduction, column 2). Hammer et al. (Journal of Animal Science, 1986) disclose the production of transgenic mice, sheep and pigs; however only mice exhibited an increase in growth due to the expression of human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth).

The above art clearly establishes that the level and the specificity of expression of a transgene as well as the phenotype of the transgenic animal thus produced are greatly dependent of the **specific** transgene construct used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are all important factors in controlling the expression of a transgene. The prior art has demonstrated that mammary specific regulatory regions can reproducibly direct a protein of

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interest to the milk, blood, or urine of a representative number of transgenic mammals (see USPN 5,880,327, for example). However, this is the exception to the unpredictable transgenic art and has not been found to be the norm as is supported by the references cited above. Additionally, the prior art taught that Uroplakin II is a urine specific promoter which can be used to produce proteins in transgenic mice (see USPN 5,824,543). However, neither the specification nor the prior art teaches that regulatory regions other than mammary specific regulatory regions can produce proteins in the urine in a representative number of mammals. Furthermore, neither the specification or the prior art has taught that mammalian regulatory regions can be used without undue experimentation to produce proteins in the urine in animals other than mammals.

Applicant's specification teaches that the whey acidic promoter (WAP) promoter can produce protein in the urine of pigs and mice. However, WAP is known in the art to preferentially express protein to the mammary glands of mammals (see the specification page 36 and USPN 5,880,327), such that it can be classified as a mammary specific promoter. The specification fails to provide any working examples which indicate that other promoters can reproducibly be used to express protein in the urine of any and all animals such that the skilled artisan could practice the claimed invention in the unpredictable transgenic art without undue experimentation. Therefore, given the absence of working examples for regulatory regions other than WAP, the breadth of the claims to any and all 5' regulatory regions, the unpredictable nature of the transgenic art in obtaining the desired phenotype (ie. that of expressing protein in urine at detectable levels) with any and all 5' regulatory regions, the amount of experimentation necessary to determine which regulatory

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regions would produce the desired phenotype, and the absence of teachings in the prior art to regulatory regions other than mammary specific regulatory regions, the claimed invention is limited to a non-human transgenic mammal whose genome comprises an nucleic acid sequence comprising a mammary specific promoter operably linked to a gene encoding a protein of interest, wherein expression of said protein by somatic cells in said transgenic mammal results in the production of said protein in the urine of said transgenic mammal; or a transgenic mouse whose genome comprises an nucleic acid sequence comprising a uroplakin II promoter operably linked to a gene encoding a protein of interest, wherein expression of said protein by somatic cells in said transgenic mouse results in the production of said protein in the urine of said transgenic mouse; and methods of producing the same.

Claims 52, 53, 62, and 63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of

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ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116).

With respect to claims directed to producing a transgenic animal using a uromodulin, a renin, a erythropoietin, a uropontin, a nephrocalcin or a aquaporin regulatory region, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In the instant case applicant’s specification only discloses primer regions which could be used to isolate the promoter region for the uromodulin gene. The specification does not disclose the nucleic acid sequence for the uromodulin promoter. Nor does the specification disclose the nucleic acid sequence for a 5' expression regulatory sequence to a renin gene, a erythropoietin gene, a uropontin gene, a nephrocalcin gene or a aquaporin gene.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF’s were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

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Therefore, none of the claims encompassing regulatory region to a uromodulin gene, a renin gene, a erythropoietin gene, a uropontin gene, a nephrocalcin gene or a aquaporin gene meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5-8, 11-13, 15 and 45-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5-8, 11-13, 15 and 45-65 are indefinite because the term "kidney-specific promoter" is unclear as to its metes and bounds. It is unclear if the term "kidney-specific promoter" is to encompass any promoter which can produce protein in the urine, or encompasses promoters that are derived from kidney gene function in some manner.

Claim 64 is indefinite because it recites "The method of claim 56", however, claim 56 is a product claim.

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Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 45-49, 51, 52, 54-59, 61, 62, and 64-65 are rejected under 35 U.S.C. 102(e or a) as being anticipated by Sun (USPN 5,824,543; PTO-1449 A1) or Sun et al. (WO 96/39494; PTO-1449 B3), respectively.

Sun (USPN 5,824,543; PTO-1449 A1) teaches transgenic mice whose genome comprises a uroplakin promoter operably linked to a gene of interest, wherein said gene of interest is expressed in the urothelium of said mouse and the protein is detectable in the urine of said mouse (see entire patent). At column 2, lines 25-30, and column 6, lines 5-6, Sun teaches that the protein can be isolated from the urine. At column 4, lines 57-65, Sun teaches that the protein is detectable in the urine. At column 5, lines 58-67, Sun discloses various proteins which can be expressed in the urine of transgenic mice. Thus, the claimed invention was anticipated by Sun.

Sun et al. (WO 96/39494; PTO-1449 B3) taught transgenic mice whose genome comprises a uroplakin promoter operably linked to a gene of interest, wherein said gene of

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interest is expressed in the urothelium of said mouse and the protein is detectable in the urine of said mouse (see entire patent). At page 2, Sun et al. teaches that the protein can be isolated from the urine. At page 3 and 7-8, Sun et al. teaches that the protein is detectable in the urine. At page 9, Sun et al. discloses various proteins which can be expressed in the urine of transgenic mice. Thus, the claimed invention was anticipated by Sun et al.

Claims 45-49, 51, 54-59, 61, 64 and 65 are rejected under 35 U.S.C. 102(e) as being anticipated by Lubon et al.

Lubon et al. taught a transgenic mammal comprising a mammary gland specific promoter to express protein in the milk or urine of a mammal to isolate the protein (see entire patent). At column 5, lines 52-59 and column 6, lines 45-52, Lubon et al. specifically discloses that protein can be produced in the urine. Thus, the claimed invention was anticipated by Lubon et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

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commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5-8, 11-13, 15, 45-52, 54-62, and 64-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of Sun (USPN 5,824,543; PTO-1449 A1) or Sun et al. (WO 96/39494; PTO-1449 B3) and Lubon et al. (USPN 5,880,327).

Sun (USPN 5,824,543; PTO-1449 A1) teaches transgenic mice whose genome comprises a uroplakin promoter operably linked to a gene of interest, wherein said gene of interest is expressed in the urothelium of said mouse and the protein is detectable in the urine of said mouse (see entire patent). At column 2, lines 25-30, and column 6, lines 5-6, Sun teaches that the protein can be isolated from the urine. At column 4, lines 57-65, Sun teaches that the protein is detectable in the urine. At column 5, lines 58-67, Sun discloses various proteins which can be expressed in the urine of transgenic mice.

Sun et al. (WO 96/39494; PTO-1449 B3) taught transgenic mice whose genome comprises a uroplakin promoter operably linked to a gene of interest, wherein said gene of interest is expressed in the urothelium of said mouse and the protein is detectable in the urine of said mouse (see entire patent). At page 2, Sun et al. teaches that the protein can be isolated from

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the urine. At page 3 and 7-8, Sun et al. teaches that the protein is detectable in the urine. At page 9, Sun et al. discloses various proteins which can be expressed in the urine of transgenic mice.

Lubon et al. taught a transgenic mammal comprising a mammary gland specific promoter to express protein in the milk or urine of a mammal to isolate the protein (see entire patent). At column 5, lines 52-59 and column 6, lines 45-52, Lubon et al. specifically discloses that protein can be produced in the urine.

The above teachings differ from the claimed invention in that they do not teach a transgenic mammal whose genome comprises a protein of interest wherein the protein of interest detoxifies or degrades organic material. However, given the teachings of Sun or Sun et al. which teaches that one can secrete any biologically active protein in the urine for isolation, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce any protein of interest known in the art for mass production of the protein with a reasonable expectation of success. Thus, the claimed invention was *prima facie* obvious in the absence of evidence to the contrary.

Claims 52, 53, 62, and 63 are free of the prior art, but are subject to other rejections.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen M. Hauda whose telephone number is (703) 305-6608. ✓

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, may be reached at (703) 308-2035.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Karen M. Hauda

Karen M. Hauda
Patent Examiner

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING
NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached marked-up copy of the "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).
- ☐ 7. Other: _____

Applicant must provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123 -

For CRF submission help, call (703) 308-4212

For PatentIn software help, call (703) 308-6856

Please return a copy of this notice with your response.